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Molecular Mapping of the Edwards Syndrome Phenotype to Two Noncontiguous Regions on Chromosome 18

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Summary

In an effort to identify regions on chromosome 18 that may be critical in the appearance of the Edwards syndrome phenotype, we have analyzed six patients with partial duplication of chromosome 18. Four of the patients have duplications involving the distal half of 18q (18q21.1-qter) and are very mildly affected. The remaining two patients have most of 18q (18q12.1-qter) duplicated, are severely affected, and have been diagnosed with Edwards syndrome. We have employed FISH, using DNA probes from a chromosome 18–specific library, for the precise determination of the duplicated material in each of these patients. The clinical features and the extent of the chromosomal duplication in these patients were compared with four previously reported partial trisomy 18 patients, to identify regions of chromosome 18 that may be responsible for certain clinical features of trisomy 18. The comparative analysis confirmed that there is no single region on 18q that is sufficient to produce the trisomy 18 phenotype and identified two regions on 18q that may work in conjunction to produce the Edwards syndrome phenotype. In addition, correlative analysis indicates that duplication of 18q12.3-q22.1 may be associated with more severe mental retardation in trisomy 18 individuals.

Introduction

Edwards syndrome, or trisomy 18, is the second most common autosomal trisomy, with an incidence of 1 in 8,000 live births. Most authorities consider trisomy 18 to be a fatal, congenital disorder with mean survival of 1–3 mo. Only 10% survive past 1 year of life. Congenital heart disease is the major cause of death (Van Dyke and Allen 1990). While variability in the expression and severity of associated features exists, there are hallmark features present in a majority of trisomy 18 patients. These features include mental and developmental delay, growth deficiency, abnormal craniofacial profile, clenched hands with overlapping digits, internal organ malformations including inguinal or umbilical hernias, and multiple congenital heart defects (Jones 1988, pp. 16–19; Binkert et al. 1990). Phenotypic variability within an aneuploid syndrome, as well as overlap in clinical features present in different syndromes, are well-known characteristics of chromosome aneuploidy. These characteristics compound the difficulty in establishing a succinct correlation between aneuploidy for a specific chromosome region and the manifestation of specific traits (Wilson 1990). In fact, phenotypic variability has led to disagreement over specificity versus nonspecificity in the pathogenesis of aneuploid phenotypes, including trisomy 18 and trisomy 21 (Neu et al. 1976; Epstein 1988).

While the trisomy 18 phenotype is most often associated with duplication of the entire chromosome, a number of cases reflect individuals carrying partial duplications of different regions of chromosome 18. The clinical manifestations in these individuals range from a relatively mild to a severe phenotype. Some exhibit extreme mental and developmental retardation with most of the key physical malformations seen in trisomy 18 (Fryns et al. 1978; Matsuoka et al. 1981). Others exhibit a relatively mild phenotype and lack key determinants of the syndrome (Turleau and de Grouchy 1977; Fryns et al. 1979; Turleau et al. 1980). These patients are useful in determining whether associations exist between the expression of a particular phenotypic feature and a specific chromosome region that has been duplicated. A precise genotype-phenotype correlation will ultimately lead to the identification of genes on chromosome 18 whose increased dosage might be responsible for specific features of Edwards syndrome. This strategy has been pursued in the molecular dissection of the Down syndrome phenotype. Many Down syndrome features, including facial features, some of the hand and foot abnormalities, and some dermatoglyphic features, have been assigned to a 3.7-Mb region within band 21q22.2 or adjacent 21q22.1 (Korenberg et al. 1992). The congenital

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heart defects and duodenal stenosis associated with Down syndrome have been mapped to overlapping regions of ~5 Mb and ~26 Mb, respectively (Korenberg et al. 1992).

At this time less progress has been made in elucidating the molecular aspects of Edwards syndrome. While several cases of partial trisomy 18 appear in the literature, the extent of duplication in most reports is based solely upon cytogenetic analysis of metaphase chromosomes, making a precise determination impossible. This may account for the inability to reach a consensus on whether a critical region exists in Edwards syndrome and, if so, in what region. Proposed critical regions include the region proximal to band 18q12.2 (Muecke et al. 1982), band 18q21 (Matsuoka et al. 1981), and 18q11 in combination with 18q22-qter (Turleau and de Grouchy 1977).

Recently Mewar et al. (1993*b*) began a systematic molecular analysis of patients with partial duplications of chromosome 18. On the basis of molecular analysis of the extent of chromosome 18 duplication in these patients, region 18q11 was ruled out as a candidate critical region in Edwards syndrome. The involvement of either the distal portion of 18q or multiple, noncontiguous regions that lie distal to 18q11 was suggested. The present report characterizes an additional six patients, using FISH to precisely define the extent of chromosome 18 duplicated in each patient. We have correlated the extent and region of chromosomal duplication with those features most representative of the Edwards syndrome phenotype. Our analysis supports the hypothesis that duplications of both proximal and distal regions are critical to the Edwards syndrome phenotype. Furthermore, genotype:phenotype correlation based on our patients and those previously reported by Mewar et al. (1993*b*) indicates that severe mental retardation may be associated with duplication of region 18q12.3-q21.1.

Material and Methods

Cytogenetic Analysis and Cell Lines

Prometaphase chromosomes were prepared from stimulated peripheral blood lymphocytes after synchronization with excess thymidine. Chromosomes were G-banded using trypsin and Giemsa stain according to standard protocols (Verma and Babu 1989, pp. 47–49). Chromosomes are described according to ISCN nomenclature. Lymphoblastoid cell lines were established from whole blood according to standard procedures.

FISH

FISH was performed using chromosome spreads prepared from both peripheral blood lymphocytes and lymphoblastoid cell lines. Bacteriophage lambda clones that had been previously mapped to distinct regions on chromosome 18 by Southern hybridization to somatic cell hybrid panels (Kline et al. 1992, 1993) were used as probes for FISH. The bacteriophage lambda clones were labeled by nick-translation with biotin-11-dUTP by using the Bionick Kit (Bethesda Research Laboratories). Hybridization and detection were performed as described elsewhere (Mewar et al. 1993*a*), with some modifications. In brief, 400 ng of labeled probe DNA was hybridized with 5 ng of sheared salmon sperm DNA and 4.5 μg of Cot-1 DNA in 50% formamide, 1 × SSC, 10% dextran sulfate. Hybridization was performed overnight at 37°C with subsequent washes in 50% formamide, 2 × SSC at 42°C, 1 × SSC at 42°C, and 0.1 × SSC at 65°C. Probe detection was performed with FITC-labeled avidin after incubation in 0.2% gelatin. Chromosomes were counterstained with propidium iodide, and photographs were taken using Kodak Ektachrome 100 film. Pooled lambda phage and individual lambda phage were cohybridized with a chromosome 18–specific centromeric probe (ONCOR) for proper chromosome identification. At least 30 metaphases were examined for the presence or absence of probe duplication. Those lambda phage determined to be duplicated gave two signals in 90% of the cells analyzed. Lambda phage present in one copy in each homologue gave a single signal in all metaphase spreads analyzed.

Results

Case Reports

Case 1.—This patient has been described elsewhere (Lewkonia et al. 1980). In brief, this 31-year-old male was the 6-pound 4-ounce product of a full-term uncomplicated pregnancy. Poor feeding and failure to thrive were apparent within the first few months of birth. Surgery was performed to correct a congenital strabismus and undescended testes in early childhood. The patient's milestones were delayed. The patient is mildly mentally retarded. Physical examination reveals short stature, with a height appropriate for a 12-year-old and a head circumference at the 98th percentile. The patient has frontal and parietal balding, which began at age 18 years. In addition, the upper limbs showed bilateral cubitus valgus and prominent metacarpal phalangeal joint of both thumbs, as well as bilateral clinodactyly. The patient is currently receiving medical attention for behavioral problems. Cytogenetic analysis of this patient showed partial trisomy of chromosome 18, with a direct duplication. His karyotype is 46,XY,dir dup(18)(q21.1-q22.2).

Case 2.—This female child has been developmentally delayed since birth. Physical examination at age 11 mo revealed features suggestive of Edwards syndrome. She does suffer from a slight hearing loss and choking episodes of unknown cause. The father has a balanced translocation, t(15;18)(q11.2;q11.2), which the daughter has inherited. In addition, she has 47 chromosomes as a result of a 3:1 nondisjunction of the der(15) chromosome, making her trisomic for a large portion of 18q. Her karyotype is 47,XX,t(15;18)(q11.2;q11.2),+der(15)t(15;18).

Case 3.—This male child was born 42 wk after a normal pregnancy. He was born with an omphalocele and several other Edwards syndrome malformations. The mother carried a balanced translocation, which was inherited by the patient in an unbalanced nature. The mother's karyotype is 46,XX,t(14;18)(p11.2;q11.2).

Case 4.—This female patient was delivered by Cesarean section, because of fetal distress, after an uneventful pregnancy. She was born with an omphalocele, which was surgically corrected. Gross motor milestones were within normal limits, but speech was delayed, with her first words not spoken until the age of 4 years. The patient was identified in the first grade as "learning disabled" and received special education. Recent testing at age 16 years placed her in the low-average of intelligence for age, with verbal score 89, performance score 86, and full score 87. Physical examination at age 16 years revealed very few features of Edwards syndrome. The patient received a medical workup for the recent occurrence of seizures and received special attention for emotional disturbance. A chromosome analysis of the patient revealed a karyotype of 46,XX,-18,+der(18)(qter→q21.3::p11.31→qter). Family history reveals that mother and maternal grandfather carry a pericentric inversion of chromosome 18. Thus the patient's karyotype is secondary to a crossover event. There is a maternal uncle who has $18q^-$ syndrome (Wertelecki and Gerald 1971; Vogel et al. 1990).

Case 5.—This male patient was born after an uncomplicated pregnancy. Multiple minor abnormalities apparent at birth prompted cytogenetic analysis. The patient has reportedly suffered episodes of apnea since birth and is currently being evaluated for a seizure disorder. Cytogenetic analysis has revealed a partial duplication of chromosome 18 and a partial deletion of chromosome 5. The full karyotype for this individual is 46,XY,-5, +der(5)t(5;18)(p14.3;q21.1).

Case 6.—At nearly 5 years of age, this female child has physical features that include brachydactyly of the fingers and toes, dystrophic nails, mild facial asymmetry, and a small mouth. While she exhibits mild to moderate developmental delay, her growth is normal. Her medical history includes right hydronephrosis, strabismus, hyperopia, and a mild hearing loss. In addition, she has what has been described as an essential tremor. Although electroencephalograms were normal, she has a history of seizures. The karyotype of this patient is 46,XX,dir dup(18)(q21.1-qter).

A more complete comparison of the clinical findings in these six patients is shown in table 1. Partial karyotypes are shown in figure 1. For cases 2 and 3, the cytogenetic and molecular analysis was performed using samples from the balanced-translocation parent.

Molecular Cytogenetic Analysis

To determine the extent of chromosome 18 duplication in these six individuals, a FISH-based approach was utilized because of the availability of a high-resolution physical map for chromosome 18 (fig. 2). Chromosome 18 has been divided into 29 contiguous regions, each containing

Table 1

Clinical Features of Patients with Partial Duplication of Chromosome 18

	Case					
	1	2	3	4	5	6
Duplicated region	q21.1-q22.2	q11.2-qter	q11.2-qter	q21.3-qter	q21.1-qter	q21.31-q23
Age at evaluation	31 years	2 years	18 mo	16 years	4 mo	5 years
Fetal growth retardation	−	−	+	−	−	−
Failure to thrive	+	−	+	−	+	−
Mental retardation	+	++	++	+	+	+
Developmental delay	+	++	++	+	+	+
Prominent occiput	−	+	+	−	−	−
Short/slanting palpebral fissures	−	+	+	−	−	−
Low-set/abnormal ears	+	−	+	−	−	−
High-arched/cleft palate	−	+	+	+	−	−
Micrognathia	−	+	+	+	+	−
Short sternum	−	−	+	−	−	−
Overlapping digits	−	+	+	−	−	−
Abnormal dermatoglyphics	−	NK	NK	−	NK	NK
Abnormal genitalia	+	−	+	−	−	−
Short hallux	−	+	+	−	−	−
Congenital heart defect	−	−	+	−	+	−
Hernia	−	−	+	+	−	−
Edwards syndrome	−	+	+	−	−	−

NOTE.—+ = present; − = absent; and NK = not known.

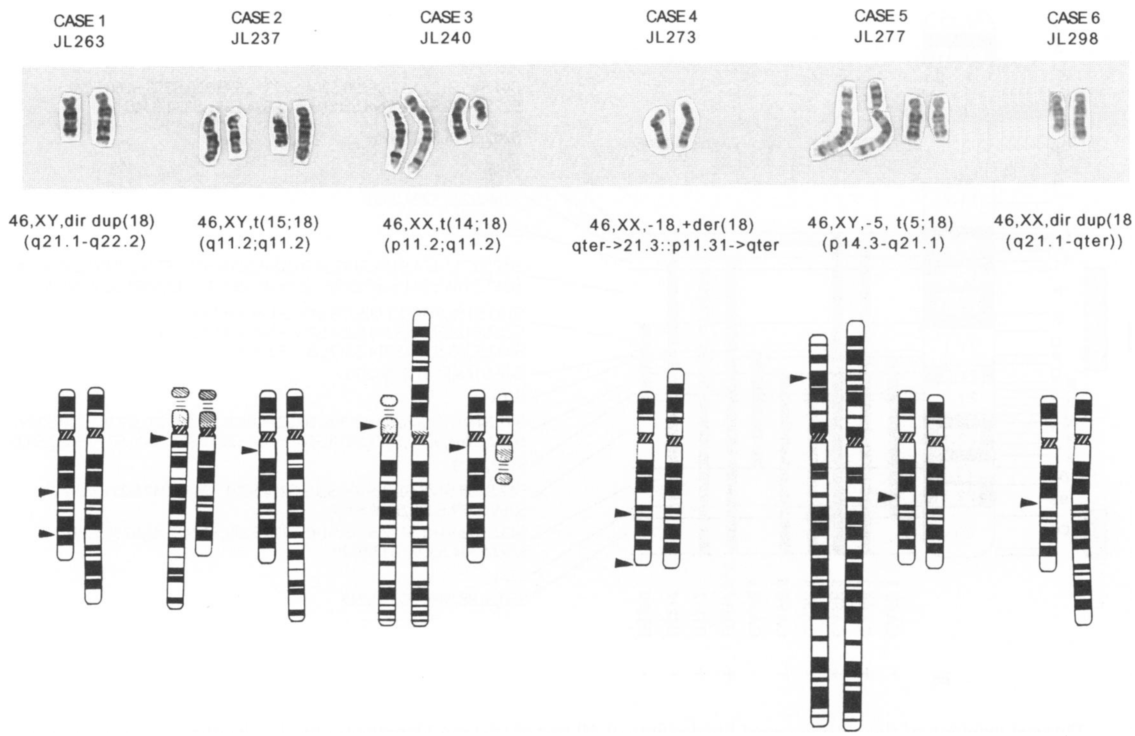

Figure 1 Partial karyotypes including the derivative chromosomes of the six partial trisomy 18 cases. Ideograms showing the cytogenetically determined breakpoints are shown.

1–25 bacteriophage lambda clones. Individual clones within these regional pools have not been ordered with respect to each other. The strategy that was utilized involved the initial screening of chromosomes with those regional pools of labeled phage clones that mapped to the cytogenetically determined breakpoint region. When a region containing the breakpoint was identified, all phage clones within that region were individually hybridized to the chromosomes to define the precise location of the breakpoint within that region.

Examples from the analysis of case 1 are shown in figure 3. Standard cytogenetic analysis suggested that the chromosomal region 18q21.1-q22.2 was duplicated in this patient. Thus, FISH analysis using phage clones in region M and region N (fig. 2) was performed. Only a single signal on the dup(18) was observed in each case, suggesting a more distal duplication. The pool of phage clones from region O also showed a single fluorescent signal on the dup(18) (fig. 3*a*). In contrast, hybridization of pooled DNA from region P indicated that this region was duplicated. Examples from the subsequent hybridizations of individual lambda phage from regions O and P are shown in figure 3*b* and *c*, respectively. These analyses determined that the chromosomal breakpoint for the duplication mapped between regions O and P. That is, all the phage clones in region O were present in single copy, while all the lambda clones in region P were present in two copies on the dup(18). The proximal duplication breakpoint was thus determined to be at 18q21.1. As expected, hybridization of the pooled lambda phage from region S at 18q21.3 indicates a duplication of this region (fig. 3*d*). Similar analysis of the distal breakpoint revealed that it was located in region CC within band 18q23. This was unexpected, since the breakpoint was determined cytogenetically to be located at 18q22.2. Of the six phage mapped to region CC, only one was duplicated. These results indicate an interstitial duplication as expected; however, the duplicated region is slightly larger than initially determined by using standard cytogenetic banding approaches. The molecularly defined duplication encompasses 18q21.1-q23.

Chromosome analysis performed on the balanced-translocation–carrier parents of cases 2 and 3 revealed a t(15;18)(q11.2;q11.2) in case 2 and a t(14;18)(p11.2;q11.2) in case 3. FISH analysis in both cases revealed a more distal break on chromosome 18, at q12.1. As a result, cases 2 and 3 inherited a smaller duplication of chromosome 18 than was previously determined. The duplicated region for both involved 18q12.1-qter. In case 2 the chromosome 18 breakpoint was found within region J, while in case 3 the breakpoint was located more proximally in region I. Case 3 thus inherited a slightly larger duplication.

Karyotypic analysis of case 4 revealed a partial duplication of the long arm of chromosome 18 and a partial deletion of the short arm in a der(18)(qter→21.3::

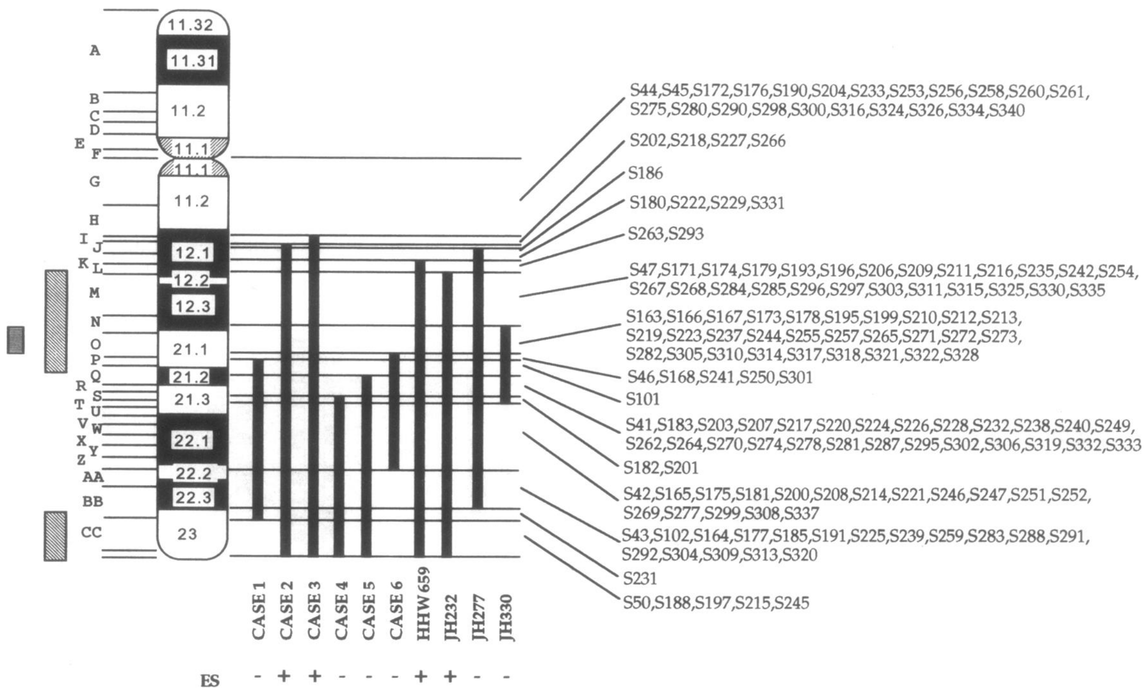

Figure 2 Physical mapping of the chromosomal breakpoints of 10 partial trisomy 18 patients, and localization of chromosomal regions that are involved in the Edwards syndrome phenotype. An ideogram of chromosome 18 is shown. The horizontal black lines projecting from the left of the ideogram represent distinct chromosomal breakpoints that have been used to order the lambda phage clones into 29 regions, A–CC. The vertical black bars represent the chromosome 18 material duplicated in each patient. The locations of the DNA probes with respect to the duplications present in the 10 patients are shown on the right. On the far left, the two diagonally striped bars identify the regions that act in conjunction to produce the Edwards syndrome phenotype. The smaller, horizontally striped box at the far left identifies a region that has a disproportionate influence on the severe mental retardation associated with this syndrome.

p11.31→qter). In this case FISH provided a more refined breakpoint determination. Hybridization of region S lambda clones previously mapped to 18q21.31 indicated a duplication breakpoint within the region. Molecular cytogenetic analysis of this patient thus revealed duplication of the region 18q21.31-qter.

Molecular cytogenetic analysis of case 5 gave results similar to those of case 4, providing a more refined localization of the duplication endpoints. The chromosome 18 breakpoint in case 5 was localized within region P, at 18q21.1. Individual hybridization of the three lambda clones that constitute region P showed that two of these probes hybridized to the der(5), mapping them distal to the break on chromosome 18. These two probes were thus present in three copies. The remaining probe mapped proximal to the break and was therefore present in the normal copy number. On the basis of the molecular analysis, the duplicated region in this patient was determined to be 18q21.1-qter. Similar molecular cytogenetic analysis of case 6 identified the duplication as spanning 18q21.1-q2.2. A composite of the physical mapping of the chromosome 18 duplications is shown in figure 2.

Discussion

We have made use of both conventional cytogenetic analysis and FISH to determine the regions duplicated in six individuals presenting with various features of Edwards syndrome. The features that we chose to evaluate (table 1) are those present in ≥50% of affected individuals (Marion et al. 1988). The documentation of genital abnormalities was also included, although they are not commonly reported in Edwards syndrome patients.

The use of FISH in this analysis offers a relatively simple and quick method of precisely defining the extent of chromosome duplication in these individuals. The availability of a high-resolution physical map of chromosome 18 has enabled the use of this alternative to conventional dosage analysis. An obvious advantage to this method is the direct visualization of the duplicated segment. This is preferable to conventional dosage analysis in that it is not subject to potential error resulting from unequal DNA loading or from difficulty in quantitation of relative DNA intensities. In addition, the orientation of a duplicated segment can easily be determined using multicolor FISH analysis.

Our results emphasize the need for molecular characterization of chromosome abnormalities to make a concise determination of genotype:phenotype correlations. In case 1, a subtle discrepancy was noted between the cytogenetically determined breakpoint and that determined by FISH. The cytogenetic analysis had indicated that the distal breakpoint was within 18q22, but the FISH results showed

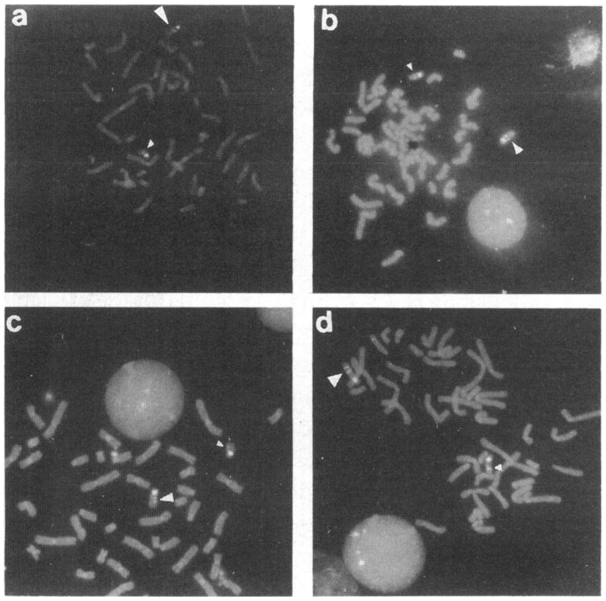

Figure 3 Localization of the chromosomal region duplicated in case 1, by using FISH. Metaphase spreads from case JL263 hybridized with various probes in addition to the chromosome 18–specific α-satellite DNA probe are shown. The small arrow points to the normal chromosome 18, and the large arrow points to the dup(18). *a*, Pool of 24 lambda clones that map to region O (18q21.1). *b*, Single lambda clone from region O (D18S210). *c*, Single lambda clone from region P (D18S101). *d*, Pooled DNA from region S.

that the duplication included part of 18q23. For cases 2 and 3, the karyotype indicated that the entire long arm of chromosome 18 was duplicated. FISH analyses revealed both breaks to be slightly more distal, at 18q12.1, indicating a smaller region of duplication. These cases point out the inherent limitations in cytogenetic analysis, particularly with respect to the resolution needed to identify bands involved in rearrangements. Chromosome length and morphology, as well as difficulty in making a distinction between chromosome bands or regions that are similar in appearance, can contribute to the imprecision. FISH provides a relatively easy and rapid method of refining or correcting initial cytogenetic observations. Even within a single cytogenetically discernible chromosome band, FISH offers a high degree of resolution. This is illustrated by the ability to order the chromosome 18 breakpoints in cases 2 and 3 relative to each other within band 18q12.1. Cytogenetically, no distinction could be made between the two breaks. Molecular analysis, however, localized the break in case 2 as being distal to that in case 3. The accurate mapping of the breakpoints with respect to each other will be crucial in the phenotypic mapping of the Edwards syndrome clinical features to discrete loci on the chromosome.

As indicated earlier, there is no consensus in the literature about the location of a critical region for Edwards syndrome. One report concluded that the critical region encompasses a region on 18q, proximal to 18q12 (Muecke et al. 1982), while another report offers an opposing view that the critical region lies in distal 18q, involving band q21 (Matsuoka et al. 1981). A composite of these theories also exists, implicating noncontiguous, proximal and distal regions in the presentation of the key features of Edwards syndrome (Turleau and de Grouchy 1977).

Our present work expands on the number of individuals reported with molecularly defined partial duplications of chromosome 18. Our cases, as well as four previously reported cases, are shown in figure 2. Our analyses support the conclusion of Mewar et al. (1993*b*)—i.e., that a region proximal to 18q12 cannot be considered critical to the Edwards syndrome phenotype. We add two cases (case 2 and case 3) to those previously reported (HHW659 and JH232), as exhibiting the classical Edwards syndrome phenotype whose duplication does not extend to band 18q11.2.

While it has been suggested that both proximal and distal regions are critical in Edwards syndrome, our data provide molecular support for this hypothesis. Comparison of the extent of duplication in these 10 individuals reveals that individuals expressing the classic Edwards syndrome phenotype contain duplications spanning both proximal and distal regions of 18q (HHW659, JH232, case 2, and case 3). The region duplicated in all these individuals is 18q12.1-qter. Four individuals not expressing the classic phenotype are trisomic for either proximal or distal segments, but not for both regions (JH277, JH330, case 4, and case 5). The breakpoint in JH277 is proximal to those present in two of the individuals showing the severe Edwards syndrome phenotype. This patient must therefore be trisomic for the proposed proximal critical region. The fact that this individual does not express the severe phenotype suggests that trisomy for an additional region is also necessary to elicit the full phenotype. When the region proximal to 18q12.1 is disregarded, JH277 is trisomic for all of 18q except 18q23, implicating this region as a second critical region for Edwards syndrome. The duplicated regions present in case 4 and case 5 extend through this putative second critical region but extend proximally to only 18q21.3 and 18q21.2, respectively. These individuals also do not exhibit a severe phenotype, strengthening the argument for a proximal critical region. Finally, case JH330 and case 1 are only mildly affected. The interstitial duplications present in these individuals may not contain either of the two proposed critical regions in Edwards syndrome. As shown in figure 2, on the basis of the patients whom we have analyzed, we conclude that the proximal critical region lies within 18q12.1-18q21.2 and that the distal critical region lies within 18q22.3-qter.

In addition to confirming the presence of at least two regions critical in establishing the full Edwards syndrome phenotype, our results suggest that severe mental retardation in this syndrome may be associated with trisomy for the region 18q12.3-q21.1. The four patients described in our previous report (Mewar et al. 1993*b*), as well as case 2 and case 3 in the present study, are all severely mentally retarded. These six individuals show a common region of duplication, 18q12.3-q21.3. We have narrowed this region to exclude distal 18q21.1-q21.3, since none of the four remaining individuals with duplications within this region show severe mental retardation.

The ideal situation for establishing a phenotypic map of Edwards syndrome is the analysis of individuals showing pure partial trisomy for chromosome 18. The presence of aneuploidy for other chromosome regions complicates the clinical interpretation. Ten individuals have been considered here. Of these 10 individuals, 4 are pure partial trisomies for chromosome 18 (case 1 and case 6 from the present study and case JH277 and case JH330 from the previous study). A fifth individual, case 4, has a small deletion of 18p, in addition to partial trisomy of 18q. Patients with $18p^-$ syndrome have a clinical phenotype that includes short stature, epicanthal folds, short fingers, and syndactyly and usually have loss of the entire short arm of chromosome 18 (Zumel et al. 1989). Our patient has short stature (height appropriate for an 11-year-old) and a hand length appropriate for her short stature. Since our patient has only a small deletion with a few features of the $18p^-$ syndrome, this case poses minimal complication because of a second aneuploidy. Similarly, case 2 and case 3 in our study and case JH232 from the previous study, showing additional partial deletions within satellite DNA, pose little if any concern, since satellite deletions usually elicit no phenotype. In case HHW659 and case 5, monosomy for chromosome 5p is present in addition to partial duplication of 18q. The 5p deletion present in case HHW659 does not remove the cri-du-chat critical region at 5p15.2 (Overhauser et al. 1994). This individual displays few features of the cri-du-chat syndrome, while her phenotypic features are suggestive of Edwards syndrome. Case JL277 does carry a deletion of the cri-du-chat critical region, and his clinical features are more suggestive of this syndrome. He exhibits only a few of the typical Edwards syndrome features. The possibility exists that the expression of double aneuploidy in this individual has altered the phenotypic expression of those features representative of Edwards syndrome. For the most part, however, our patients seem to be free of the complicating factors of additional aneuploidy.

Difficulties in establishing a precise correlation between genotype and phenotypic expression in a given aneuploid syndrome are twofold. First, the complexity and variation in clinical presentation of these syndromes necessitates the establishment of strict guidelines for the documentation of patient phenotype. Such guidelines, as have been developed for obtaining and recording pertinent information in Down syndrome patients (Korenberg et al. 1992), are critical to establishing the correct genotype-phenotype correlations. Second, there is a need for molecular evaluation of the extent of duplication/deletion in aneuploid syndromes. Cytogenetic analysis alone may be insufficient for a precise determination of the chromosome alteration.

It has been proposed that the phenotypic expression in aneuploid syndromes is the cumulative result of the imbalance of distinct genetic loci within the aneuploid region (Epstein 1988). While some features may be the result of interacting loci from contiguous or noncontiguous regions, others may result from the altered dosage of a single gene. This model does not rule out the possibility that altered dosage of one gene may be responsible for multiple features, enabling small regions of imbalance to elicit complex phenotypes. Stochastic and environmental factors may also contribute to the phenotypic variability in these syndromes. An alternate model stresses a more generalized disruption of evolved genetic balance in the etiology of aneuploid phenotypes (Shapiro 1989). This model suggests that decreased developmental and physiological buffering, as a result of chromosome imbalance, may limit morphogenic control and developmental stability. In this model, variability within a syndrome is attributed to nonspecific environmental factors. Similarity between syndromes is explained by the general perturbation of traits that are developmentally less controlled and, therefore, more likely to be affected by genetic imbalance, regardless of the origin of imbalance. This second hypothesis has yet to be disproved; however, it fails to account for the ability to clinically diagnose the various aneuploidies in spite of some overlap in clinical features.

Phenotypic mapping is the first step in elucidating the genetic basis of clinical expression in these syndromes. It may be that neither hypothesis—either that based on general instability or that based on distinct genetic loci—is entirely correct. Support for the less-generalized hypothesis however, has been provided by the recent molecular mapping in Down syndrome. Mapping of several of the characteristic features to a region in band 21q22, below the level of cytogenetic resolution (Korenberg et al. 1992), may be the first step in localizing gene(s) directly responsible for these features. It is expected that, with the analysis of many more patients with partial duplication of the long arm of chromosome 18, along with the obtainment of more extensive clinical descriptions, genotype:phenotype correlations that are of the extent of those available for Down syndrome can be accomplished for Edwards syndrome.

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